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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/765,104	01/16/2001	Anne N. Murphy	660088.438	8241

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EXAMINER	
SIEW, JEFFREY	
ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 01/09/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/765,104	MURPHY ET AL.	
	Examiner	Art Unit	
	Jeffrey Siew	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 January 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-96* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-96* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *1/16/01* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Oath/Declaration

1. The oath/declaration is objected for being unsigned by the second inventor Amy K. Stout.

Drawings

2. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

3. The labeling in the Graph of Figure 7-13 A is difficult to read. Correction is required.

Specification

4. In the Brief Description of Drawings Figure 13 is described but the Drawings contain a Figure 13A and 13B. Appropriate correction is required.

5. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (e.g. see page 31 line 11 & pg 70 line 23, 73 lien 12). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Objections

6. Claims 46 & 48 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 43 already recites a calcium ionophore which is a compound that alters intracellular distribution of calcium cation.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-96 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-96 are indefinite because it is unclear as to whether the agent refers to the cytosol or previously recited reagent or another reagent yet to be added.

B) Claims 19-21 , 40-42 & 60-62are indefinite because in step 3 the designation (i) and (ii) are unclear. It cannot be determined whether they refer to biological sample and source of calcium cations or substeps.

C) Claims 63-79 are indefinite because it is unclear as to what the term "depleted of cytosol" entails when the cell contains mitochondria a component of cytosol.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 22,24-26,28-30,33,34,37,39,41,42,63 & 81 rejected under 35 U.S.C. 102(b) as being anticipated by Matlib (JBC vol. 273 No. 17 pp. 10223-10231 1998).

Matlib et al teach the assay of the effect of ruthenium amine complex and Ru360 on Ca++ uptake in mitochondria in vitro and in situ in single cardiac myocytes (see whole doc. esp. abstract). They teach that Ruthenium Red and Ru360, a known inhibitor of Ca++ uniporter which are expressed in cells inhibited uptake. They prepared mitochondria by isolated by centrifugation. They also prepared the cells with digitonin permeabilization and placed cells on a stage in inverted microscope(see page 10224). In Figure 2 they measure different concentrations of ruthenium red in zero concentration and increasingly greater concentration. The increased

concentration of either Ru360 or Ruthenium Red led to greater inhibition of uptake. They also performed time studies over time showing the effect of Ru350 on myocytes and mitochonidria (see figure 8 & 9). They measure calcium uptake by spectrophotometrically using arsenazo III (see page 10224).

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 23,27,31,38,40,60,61 & 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matlib (JBC vol. 273 No. 17 pp. 10223-10231 1998) in view of McCormack et al (Biochimica et Biophysica Acta vol. 973 no. 420-427 1989 pp. 420-427).

The teachings of Matlib are described previously.

Matlib et al do not teach further adding an ionophore nor contacting with Ca++ more than once.

McCormack et al teach the use of ionomycin which equilibrates the matrix and extramitochondria and FCCP an uncoupler to equilibrate the protons (see page 422) and they teach the effects of increasing Ca++ in mitochondria (see figure 4).

One of ordinary skill in the art would have been motivated to add ionomycin to permeabilize the mitochondria in order increase Ca++ stabilization. McCormack et al states that ionomycin equilibration would allow more accurate Ca++ value calculation. It would have been prima facie obvious to apply McCormick et al's teaching of ionomycin and FCCP so that an accurate measure of Ca++ concentration would be achieved.

Moreover it would have been prima facie obvious to apply McCormick et al's teaching of repeated contact with increasing Ca++ to Matlib et al's assay in order to examine the effect of increasing extramitochondrial Ca++ concentration.

10. Claims 1,3-9,12,13,16-21,54 ,55, 58,59,64-66,68,69,71,74,75,78-80, 82,83, 85,86,89 & 90 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matlib (JBC vol. 273 No. 17 pp. 10223-10231 1998) in view of Marban et al (US6,183,948 Feb. 6, 2001).

The teachings of Matlib are described previously.

Matlib et al do not teach high throughput assay.

Marban et al teach of high through put screening for testing a range of chemicals in mitochondrial effects (see col. 8 line 3-10).

One of ordinary skill in the art would have been motivated to apply Marban et al's teaching of high throughput assays in order to screen multiple reagents and different concentrations and their effects of Ca++ uptake. As it was well known and commonly practiced in the art to employ high throughput assays to examine a plurality of samples quickly, it would have been prima facie obvious to apply Marban et al's teaching of high throughput methods to Matlib et al's assay in order to screen many samples for their effect of Ca++ uptake in mitochondria.

11. Claims 2,10,43-52,54,55,58,59,67,70,72,84,87,93 & 96 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matlib (JBC vol. 273 No. 17 pp. 10223-10231 1998) in view of Marban et al (US6,183,948 Feb. 6, 2001) in further view of McCormack et al (Biochimica et Biophysica Acta vol. 973 no. 420-427 1989 pp. 420-427).

The teachings of Matlib are described previously.

Matlib et al do not teach further adding an ionophore.

McCormack et al teach the use of ionomycin which equiblibrates the matrix and extramitochonidra and FCCP an uncoupler to equilibrate the protons (see page 422).

One of ordinary skill in the art would have been motivated to add ionomycin to permeabilize the mitochondria in order increase Ca++ stabilization. McCormack et al states that ionomycin equilibration would allow more accurate Ca++ value calculation. It would have been

prima facie obvious to apply McCormick et al's teaching of ionomycin and FCCP so that an accurate measure of Ca++ concentration would be achieved.

12. Claims 94 & 95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matlib (JBC vol. 273 No. 17 pp. 10223-10231 1998) in view of Marban et al (US6,183,948 Feb. 6, 2001) and McCormack et al (Biochimica et Biophysica Acta vol. 973 no. 420-427 1989 pp. 420-427) in further view of Bernardi et al (JBC vol. 268 1993 pp. 1005-1010).

The teachings and suggestions of Matlib, Marban, McCormack et al are described previously.

Matlib et al do not describe cyclosporin.

Bernardi et al teach the effect of cyclosporin on MTP transition pore with Ca__ ions (see whole document.)

One of ordinary skill in the art would have been motivated to apply Bernardi et al's cyclosporin A to Matlib et al's assay in order to examine the effect of cyclosporin on the Calcium uptake. It would have been prima facie obvious to apply Bernardi et al's cyclosporin A in Matlib et al's assay so that the MTP inhibitory effect on calcium uptake would be examined.

13. Claims 11,14, 32,35,88 & 91 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matlib (JBC vol. 273 No. 17 pp. 10223-10231 1998) in view of Marban et al (US6,183,948 Feb. 6, 2001) in further view of Murphy et al (PNAS vol. 93 pp. 9893-9898 1996).

The teachings and suggestions of Matlib and Marban et al are described previously.

Matlib et al do not teach high bcl-2

Murphy et al teach that Bcl-2 potentiates the maximal calcium uptake capacity in mitochondria.

One of ordinary skill in the art would have been motivated to apply Murphy et al's Bcl-2 to Matlib et al's assay in order to examine the effect of calcium regulation in cell death. Murphy et al state that Bcl-2 expressing cells have an enhanced ability to sequester large concentrations of Ca++ without undergoing respiratory impairment, it would have been prima facie obvious to further use Bcl-2 expressing cells in Matlib et al's assay in order to study the calcium uptake effect on cell death.

14. Claims 53,56,73 & 76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matlib (JBC vol. 273 No. 17 pp. 10223-10231 1998) in view of Marban et al (US6,183,948 Feb. 6, 2001) and McCormack et al (Biochimica et Biophysica Acta vol. 973 no. 420-427 1989 pp. 420-427) in further view of Murphy et al (PNAS vol. 93 pp. 9893-9898 1996).

The teachings and suggestions of Matlib, Marban et al and McCormack et al are described previously.

Matlib et al do not teach high bcl-2

Murphy et al teach that Bcl-2 potentiates the maximal calcium uptake capacity in mitochondria.

One of ordinary skill in the art would have been motivated to apply Murphy et al's Bcl-2 to Matlib et al's assay in order to examine the effect of calcium regulation in cell death. Murphy

et al state that Bcl-2 expressing cells have an enhanced ability to sequester large concentrations of Ca++ without undergoing respiratory impairment, it would have been prima facie obvious to further use Bcl-2 expressing cells in Matlib et al's assay in order to study the calcium uptake effect on cell death.

SUMMMARY

15. No claims allowed but claims 15, 36, 57, 76 & 92 are free of the prior art . There is no prior art that teach or suggest the claimed method further involving transfecting with a gene encoding a calcium uniporter.

CONCLUSION

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Siew whose telephone number is (703) 305-3886 and whose e-mail address is Jeffrey.Siew@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route. The examiner is on flex-time schedule and can best be reached on weekdays from 6:30 a.m. to 3 p.m. If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703)-308-1152.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist for Technology Center 1600 whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Center numbers for Group 1600 are Voice (703) 308-3290 and Before Final FAX (703) 872-9306 or After Final FAX (703) 30872-9307.

Jeffrey Siew

January 8, 2002